

REMARKS

Claims 72-100 are pending in this application. Claims 83-86 and 97-100 are withdrawn from consideration as being directed to a non-elected invention. Claims 78, 79, 92 and 93 are canceled without prejudice. Applicants reserve the right to pursue the subject matter of the canceled claims in one or more related applications.

Claims 72, 76 and 87 have been amended to clarify certain embodiments of the presently claimed invention. Support for the amendments can be found in the specification as originally filed at, *inter alia*, [0004] at page 2, line 3; [0005], line 4; [0007], line 1; [0021], line 2; [0022], line 2; [0023], line 2; [0024], line 2; [0025], lines 1-2; [0039], line 2 and last line; [0041]; example 3, line 1; [00106], last line; and originally filed claims 1, 26, 34, 42 and 50.

No new matter has been added. Upon entry of the present amendments, claims 72-77, 80-91, and 94-100 will be pending in the present application.

I. THE CLAIMS REJECTIONS UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

Claims 87 and 89-92 are rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Oh *et al.*, 2002, "Cucurbitacins from *Trichosanthes kirilowii* as the inhibitory components on tyrosinase activity and melanin synthesis of B16/F10 melanoma cells," Plant Med. 68:832-833 ("Oh"). For the following reasons, we disagree.

1. The Legal Standard

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Further, the anticipating reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter. *See PPG Indus., Inc. v. Guardian Indus. Corp.* 75 F. 3d 1558, 1564, 37 U.S.P.Q.2d 1618, 1623 (Fed. Cir. 1996).

It is well established that in order for a prior art reference to amount to an inherent anticipation of a claim, all the elements of the claim must *necessarily, inevitably, and always* result from the prior art disclosure and would be so recognized by one of ordinary skill in the art; mere possibilities or probabilities are not sufficient. *See Continental Can Co. USA v.*

Monsanto Co., 948 F.2d 1264, 1269, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991). As stated by the Court of Appeals for the Federal Circuit:

we are not persuaded that the 'effect' of the processes disclosed in [the prior art patents], an 'effect' undisclosed in those patents, would be always to inherently produce or be seen always to produce products meeting all of the claim limitations. Anticipation of inventions set forth in product claims cannot be predicated on mere conjecture respecting the characteristics of products that might result from the practice of processes disclosed in references.

W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 1553-1554, 220 U.S.P.Q. 303, 313-314 (Fed. Cir. 1983) (citing *In re Felton*, 484 F.2d 495, 500, 179 U.S.P.Q. 295, 298 (C.C.P.A. 1973)).

It is not sufficient that a teaching of a prior art reference *could* yield a result that would anticipate the claim against which the prior art reference is applied; instead, to be anticipatory under the doctrine of inherency, the teaching of the prior art reference *must inevitably* lead to the result. As has also been stated:

Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.

In re Oelrich, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 325-26 (C.C.P.A. 1981) (citing *Hansgirk v. Kemmer*, 102 F.2d 212, 214, 40 U.S.P.Q. 665, 667 (C.C.P.A. 1939)).

2. The Claims Are Not Anticipated By Oh

Oh discloses a method for obtaining cucurbitacin D and 23,24-dihydro-cucurbitacin D from the roots of *Trichosanthes kirilowii* Maxim (see page 833, col. 1, ¶3). However, Oh's method involves a separation step before the concentration step, and thus, concentrates a different liquor than the claimed method. Moreover, Oh's method does not include a heating step that is separate from and precedes the concentration step, as recited in claim 87. Anticipation under 35 U.S.C. § 102 requires identity of invention. *Scripps Clinic & Research Fdn. v. Genentech Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).

Oh's method requires, first, subjecting the dried roots of *T. kirilowii* to extraction with methanol, and then concentrating the methanol extract. It is reasonable to conclude that only those substances soluble in and hence extracted by methanol from the roots were

concentrated, while the residues (*i.e.*, the substances not extracted by methanol) were not concentrated. Although not explicitly stated in Oh, Applicants point out that a separation step was involved in Oh's method.

In contrast, the claimed method requires that a mixture comprising a first solvent and the plant is formed, and then the mixture is heated to form a liquor, and the liquor is subsequently concentrated. Unlike Oh, the mixture that is heated in the claimed method contains both the first solvent and the plant, and includes substances that are soluble as well as substances that are insoluble in the first solvent. Hence, the claimed method is not identical to Oh's method.

On page 3, paragraph 4, line 2 of the Office Action, the Examiner contends that the concentration step disclosed in Oh is identical to heating and forming a syrup (the stated product of the concentration step) as recited in the claimed method. However, Applicants point out that Oh does not explicitly teaches concentrating the methanol extract by heating. A concentrating step does not necessarily or inevitably involves heating. A methanol extract could have been concentrated by other means known in the art such as evaporating under vacuum, adding an adsorbent, etc. Therefore, Oh's disclosure of a concentration step does not inherently anticipates the heating and concentration steps of the claimed method.

Furthermore, even assuming *arguendo* that the concentration step in Oh's method is considered to be a teaching of the concentration step in the claimed method, the claimed method is still different from Oh's method. In this scenario, Oh's method necessarily lacks the heating step disclosed in the claimed method because the methanol extract was extracted at *room temperature* as stated in Oh (see page 833, col. 1, ¶3, lines 1-2).

Accordingly, Oh does not explicitly or inherently disclose the method steps recited in claim 87.

For the foregoing reasons, claim 87 and its dependent claims 89-92 are not anticipated by Oh. Thus, the rejection is believed to be in error and should be withdrawn.

II. THE CLAIMS REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 72-82 and 87-96 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Japanese Patent Application Publication No. 62-108844 to Iketani *et al.* ("Iketani") in view of Ozaki *et al.*, 1996, "Antiinflammatory effect of *Trichosanthes kirilowii* MAXIM, and its effective parts," Biol Pharm Bull. 19(8):1046-8 ("Ozaki"), and further in

view of Oh. The Examiner acknowledges that Iketani is deficient in various aspects, but contends that it would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention, based on the teachings of Ozaki and Oh, to arrive at the claimed invention. For the following reasons, Applicants disagree.

1. The Legal Standard

A finding of obviousness requires that “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. § 103(a). In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007), the Supreme Court rejected a rigid application of the “teaching, suggestion, or motivation” test previously applied by the Court of Appeals for the Federal Circuit. *KSR*, 127 S. Ct. at 1739, 82 U.S.P.Q.2d at 1395. However, the Supreme Court affirmed that it is “important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does...because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.” *KSR*, 127 S. Ct. at 1741, 82 U.S.P.Q.2d at 1396.

A *prima facie* case of obviousness can be established by showing a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference *and* to carry out the modification with a reasonable expectation of success, viewed in light of the prior art. Both the suggestion and the reasonable expectation of success must both be found in the prior art and *not* be based on the applicant’s disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988).

With regard to the final point, the Supreme Court in *KSR* citing *Graham*, upheld the principle of *avoiding hindsight bias* and cautioned courts to *guard against reading into the prior art the teachings of the invention in issue*. 127 S. Ct. at 1742, 82 U.S.P.Q.2d at 1397:

A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See *Graham*, 383 U.S., at 36, 86 S. Ct. 684 (warning against a “temptation to read into the

prior art the teachings of the invention in issue” and instructing courts to “guard against slipping into the use of hindsight” (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (C.A.6 1964))).

Thus, the principles set forth in *Graham* and in *Dow Chemical* – which are still good law post-*KSR* – require that *both* the suggestion and the expectation of success must be found in the prior art, and not from knowledge gained from the applicant’s disclosure.

2. The Claims Are Patentable Over Iketani In View Of Ozaki And Oh

In the Office Action, the Examiner briefly describes the teachings of Iketani (page 4, ¶3), Ozaki (page 5, ¶1) and Oh (page 5, ¶2). The Examiner acknowledges that Iketani does not disclose or teach (i) an extract from *Trichosanthes rosthornii* or *Trichosanthes japonica*; (ii) extracting with 50-70% ethanol as a first solvent; and (iii) extracting with a second solvent, such as ethanol, that has a polarity less index less than that of the first solvent (see Office Action, page 4, ¶4). However, on page 5, paragraph 3 of the Office Action, the Examiner concludes that “it would have been *prima facie* for one of ordinary skill in the art at the time the invention was made to use 50-70% ethanol from Ozaki to extract *Trichosanthes rosthornii* or *Trichosanthes japonica*, a second solvent with less polarity than the first solvent from Oh, and the right condition to isolate the effective component from HPLC.”

Applicants disagree with the Examiner for the following reasons:

First, Applicants submit that the extract included in the pharmaceutical compositions as claimed has the demonstrated ability to increase hemoglobin expression level in a cell model for studying erythroid gene expression and differentiation. The claimed compositions can be used to treat, for example, hemoglobinopathies. There is no mention whatsoever of hemoglobinopathies in the cited references. There is clearly no indication in Iketani, Ozaki, and Oh that the solvents and methods of extraction used in the respective references can be combined specifically to produce pharmaceutical compositions with the unexpected biological properties of increasing hemoglobin expression level. In fact, without Applicants’ disclosure, the problem that is solved by the present invention is not even defined by any of the cited references. One of ordinary skill in the art would not have known what relevant biological assay(s) to use to identify or characterize an extract useful in the claimed pharmaceutical compositions. Thus, the ordinarily skilled person could not have combined

the solvents and methods of Iketani, Ozaki and Oh to arrive at the claimed pharmaceutical compositions.

Second, the three references each teaches a different method for extracting different substance(s) from different parts of a *Trichosanthes* plant. In particular, Iketani extracts certain glycerol derivatives having anti-platelet aggregation activity from *Trichosanthes* seeds; Ozaki extracts certain substances with anti-inflammatory and analgesic activities from fruits and seeds; and Oh extracts certain cucurbitacin compounds having anti-tyrosinase activity from roots. A person of ordinary skill in the art would reasonably expect that *Trichosanthes* extracts containing different active ingredient(s) and displaying diverse activities would each require a different approach to extraction. Therefore, a combination of the teachings in these three references without further guidance would lead to compositions with unpredictable constituents and properties.

Moreover, there is no teachings in each of the references to suggest a combination or substitution of solvents and method steps to arrive at the claimed invention. In particular, Iketani's method for extracting 1-tricosanoyl-2,3-dilinoleoyl glycerol and 1-tricosanoyl-2-linoleoyl-3-palmitoyl glycerol comprises: (i) extracting seeds with a solvent selected from a list of at least 10 possible solvents, individually or as a mixture of unspecified proportion, to obtain a liquid extract; (ii) extracting the liquid extracts with a solvent selected from the same list plus two additional solvents, individually or as a mixture of unspecified proportion, to obtain a crude fraction; (iii) extracting the crude fraction with a solvent selected from the same list minus one solvent but plus one additional solvent, individually or as a mixture of unspecified proportion, to obtain the part containing 1-tricosanoyl-2,3-dilinoleoyl glycerol and 1-tricosanoyl-2-linoleoyl-3-palmitoyl glycerol; and (iv) extracting the part with an individual or mixture of low-boiling point solvent to obtain a mixed oil; and (v) extracting the mixed oil with an individual or mixture of some of the solvents in the list to obtain separate fractions of each glycerol derivative (see English translation, page 3, last paragraph, to page 5, first paragraph).

Iketani's five-step multi-solvent method for preparing glycerol derivatives provides no reason for one of ordinary skill in the art to look to the 50% ethanol solution of Ozaki's single-solvent method, or the methanol, n-hexane, ethyl acetate and butyl alcohol used in Oh's multi-solvent method for the extraction of specific compounds from roots. A person of ordinary skill in the art would not expect the specific steps in Oh's multi-step extraction

method to be freely interchangeable with Iketani's particular multi-step extraction method, since Iketani's compounds and Oh's compounds have different chemical structure and different polarity and would require a different approach to extraction. Thus, there is no guidance in the cited references and there are numerous combinations of solvents and method steps. The person of ordinary skill in the art would find the results of combining different solvent systems and extraction regimes each developed for obtaining different compounds from different parts of *Trichosanthes* highly unpredictable.

Furthermore, Applicants submit that the teachings of Iketani are complete for their intended purposes and, thus, a person of ordinary skill in the art would have no motivation to use a secondary reference, *i.e.*, Ozaki and/or Oh, to modify the teachings of Iketani. *In re Herschler*, 591 F.2d 693, 200 U.S.P.Q. 711 (C.C.P.A. 1979)¹.

Applicants submit that the references do not teach or suggest each and every element of the amended claims. In particular, none of Iketani, Ozaki and Oh teach or suggest an extract (i) from *Trichosanthes kirilowii* Maxim, *Trichosanthes rosthornii* Harms or *Trichosanthes japonica* Regal and (ii) which induces hemoglobin synthesis in human K562 cells, as recited in claim 72. None of the references teach or suggest an extract from a plant of *Trichosanthes* prepared by the steps recited in claim 87. Ozaki does not even teach or suggest using two solvents. A person of ordinary skill in the art at the time the invention was

¹ The Court of Customs and Patent Appeals addressed a similar situation in *In re Herschler*, 591 F.2d 693, 200 U.S.P.Q. 711 (C.C.P.A. 1979), when it held that the Board had wrongly rejected the appealed claims as obvious. In *In re Herschler*, the applicant taught the use of dimethyl sulfoxide (DMSO) to enhance transdermal penetration of a number of compounds, and claimed the process of applying to the skin a mixture comprising DMSO and a physiologically active steroid. 591 F.2d at 695, 200 U.S.P.Q. at 712. The Board rejected the claims as obvious over a primary reference (the Lubowe patent), which disclosed a hair lotion containing an estrogenic hormone and a solubilizing agent other than DMSO, combined with a secondary reference (Faust), which taught that DMSO is a safe and effective solubilizing agent for cosmetic or dermatologic use. The CCPA reversed the Board's rejection on the grounds that disclosure of the primary reference was already complete for its intended purpose, so that one of ordinary skill in the art would not have been motivated to use the DMSO of the secondary reference.

Similar to the Lubowe patent, the disclosure of Iketani is complete for its intended purpose, namely an extraction method useful to extract novel glycerol derivatives from *Trichosanthes* seeds. Because the solution is complete, Iketani provides no reason to look to the art for alternative means to extract novel glycerol derivatives, and, in particular, no motivation to look to the 50% ethanol solution of Ozaki's single-solvent system or the solvents in Oh's multi-solvent system.

made would have no reason to combine the teachings of the cited references to arrive specifically at the claimed invention. Applicants submit that the Examiner has improperly read into the prior art the teachings of the invention in issue. Such hindsight bias should be avoided. *KSR*, 127 S. Ct. at 1742, 82 U.S.P.Q.2d at 1397.

Furthermore, none of the references, either alone or together, teach or suggest a pharmaceutical composition comprising an extract from a *Trichosanthes* plant with the characteristics recited in claims 75 and 88. The Examiner contends that it is routine optimization to determine an appropriate concentration of mobile phase to purify the *Trichosanthes* extract (see Office Action, page 6, ¶3). Applicants disagree and point out that there is nothing routine in setting up a HPLC system that effectively separates the pharmaceutically active substances in the extracts of the claimed pharmaceutical compositions from the myriad of compounds present in the plant, and in identifying a profile that is characteristic of an extract that induces hemoglobin expression in human K562 cells. The position of the peak would have been completely unpredictable. None of the references cited by the Examiner contemplated the utility of treating hemoglobinopathies. There is nothing in these references to suggest that a biological assay based on induced hemoglobin expression in K562 cells be used (i) to study *Trichosanthes* compounds, and (ii) to guide the isolation and characterization of the extract in the claimed pharmaceutical compositions. The extract exhibiting the HPLC profile recited in claims 75 and 88 could not have been obtained without undue experimentation.

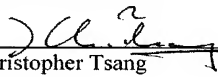
For the foregoing reasons, Applicants submit that a *prima facie* case of obviousness cannot be established based on Iketani, Ozaki and Oh. Withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants respectfully request entry of the amendments and remarks made herein into the file history of the present application. Withdrawal of the Examiner's rejections and an allowance of the application are earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

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Respectfully submitted,



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Enclosures